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Chapter 33: Central Nervous System Infections

INTRODUCTION

- *Central nervous system* (CNS) infections include a wide variety of clinical conditions and etiologies: meningitis, meningoencephalitis, encephalitis, brain and meningeal abscesses, and shunt infections. The focus of this chapter is meningitis.
- CNS infections may be caused by a variety of bacteria, fungi, viruses, and parasites. The most common causes of bacterial meningitis are *Streptococcus pneumoniae*, group B Streptococcus, *Neisseria meningitidis, Haemophilus influenzae,* and *Listeria monocytogenes*.

CLINICAL PRESENTATION

- Signs and symptoms of acute bacterial meningitis include fever, nuchal rigidity, and altered mental status. Up to 95% of patients exhibit at least two of the following symptoms: fever, nuchal rigidity, headache, and altered mental status. Kernig and Brudzinski signs may be present but are poorly sensitive and frequently absent in children.
- Clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, irritability, refusal to eat, and convulsions.
- Meningitis causes changes in fluid (CSF), and these changes can be used as diagnostic markers of infection (**Table 33-1**).
- CSF examination is essential for establishing the diagnosis of bacterial meningitis, identifying the pathogen, and performing susceptibility testing. CSF polymorphonuclear pleocytosis, an elevated CSF protein of >50 mg/dL (500 mg/L), and a CSF glucose concentration of <50% of the simultaneously obtained peripheral value suggest bacterial meningitis.
- CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80%–90% of patients with community-acquired bacterial meningitis if the CSF sample is obtained before the start of antimicrobial therapy.
- Gram stain is a rapid, inexpensive, and accurate method to assess the presence of bacteria in CSF. However, the sensitivity of the Gram stain depends on the causative microorganism and burden of disease.
- In patients with suspected CNS bacterial infection, blood cultures are strongly recommended and should be collected before the first dose of antibiotics. Blood cultures identify the causative organism in 50%–80% of cases.
- Polymerase chain reaction techniques can rapidly diagnose CNS infections and may be particularly useful in patients who have received antimicrobial therapy before lumbar puncture or have negative cultures or when the organism is fastidious or fails to grow in conventional culture.

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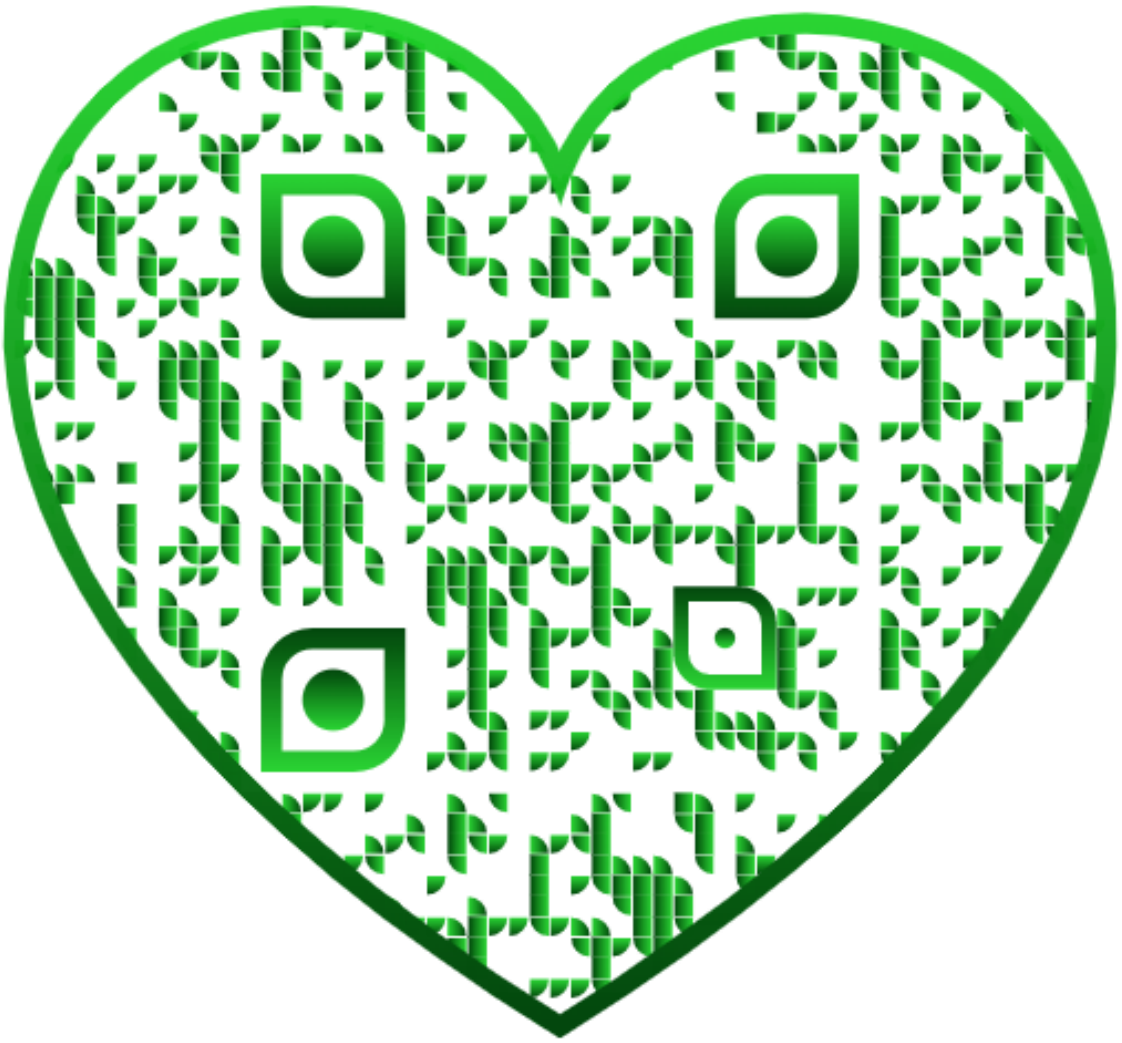

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TABLE 33-1

Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm^3 or 10^6/L)	<5 (<30 in newborns)	1000–5000	50–1000	20–500	25–500
Differential[a]	Monocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
Protein (mg/dL)	<50 (<500 mg/L)	Elevated	Mild elevation	Elevated	Elevated
Glucose (mg/dL)	45–80 (2.5–4.4 mmol/L)	Low	Normal	Low	Low
CSF/blood glucose ratio	50%–60%	Decreased	Normal	Decreased	Decreased

[a]Initial cerebrospinal fluid (CSF) white blood cell (WBC) count may reveal a predominance of polymorphonuclear neutrophils (PMNs). In CNS infection due to tuberculosis, "therapeutic paradox" may occur in which a lymphocytic predominance becomes neutrophilic during antituberculous treatment.

TREATMENT

- Goals of Treatment: Effective eradication of infection, amelioration of signs and symptoms, and reduction of morbidity and mortality.
- Key treatment elements include initiating appropriate antimicrobials, providing supportive care, and preventing disease through timely introduction of vaccination and chemoprophylaxis.
- Administration of fluids, electrolytes, antipyretics, and analgesics may be indicated for patients presenting with a possible CNS infection. Additionally, venous thromboembolism prophylaxis, antiepileptic therapy, and intracranial pressure (ICP) monitoring may be needed. Patients may require the administration of osmotic diuretics such as mannitol or hypertonic saline to maintain appropriate ICP cerebral perfusion pressure levels.

PHARMACOLOGIC TREATMENT

- Empiric antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism (**Table 33-2**). Antimicrobial therapy should last at least 48–72 hours or until the diagnosis of bacterial meningitis can be ruled out. The first dose of antibiotic should not be withheld even when lumbar puncture is delayed or neuroimaging is being performed. The time period from suspected diagnosis to initiation of antibiotic treatment should not exceed 1 hour.
- Continued therapy should be based on the assessment of clinical improvement, cultures, and susceptibility testing results. Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen.
- With increased meningeal inflammation, there will be greater antibiotic penetration (**Table 33-3**). Problems of CSF penetration can be overcome by direct instillation of antibiotics intrathecally or intraventricularly. Intraventricular delivery may be necessary in patients who have shunt infections that are difficult to eradicate or who cannot undergo the surgical management.
- See **Table 33-4** for antimicrobial agents of first choice and alternatives for treatment of meningitis caused by gram-positive and gram-negative microorganisms.
- Meningitis caused by *S. pneumoniae* has been treated successfully with 10–14 days of antibiotic therapy, while cases caused by *N. meningitidis* or *H. influenzae* usually can be treated with a 7-day course. In contrast, a longer duration (21 days or more) has been recommended for patients with *L. monocytogenes*, gram-negative or pseudomonal meningitis. Nonetheless, antibiotic treatments for bacterial meningitis should be

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individualized, and some patients may require enduring courses.

TABLE 33-2

Bacterial Meningitis: Most Likely Etiologies and Empiric Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy
<1 month	*S. agalactiae* Gram-negative enterics[a] *L. monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1–23 months	*S. pneumoniae* *N. meningitidis* *H. influenzae* *S. agalactiae* *Escherichia coli*	Vancomycin[b] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
2–50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[b] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[a] *L. monocytogenes*	Vancomycin[b] + ampicillin + third-generation cephalosporin (cefotaxime *or* ceftriaxone)

[a] *E. coli*, *Klebsiella* spp., *Enterobacter* spp. common.

[b] Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

TABLE 33-3

Penetration of Anti-infective Agents into the CSF

Therapeutic Levels in CSF with or without Inflammation of Meninges	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin
Flucytosine	Pyrazinamide
Foscarnet	Rifampin
Fosfomycin	Sulfonamides

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Ganciclovir	Trimethoprim
Isoniazid	Voriconazole
Therapeutic Levels in CSF with Inflammation of Meninges	
Ampicillin ± sulbactam	Imipenem
Aztreonam	Meropenem
Cefepime	Nafcillin
Cefotaxime	Ofloxacin
Ceftazidime	Penicillin G
Ceftriaxone	Piperacillin/tazobactam[a]
Cefuroxime	Pyrimethamine
Colistin	Quinupristin/dalfopristin
Daptomycin	Ticarcillin ± clavulanic acid[a]
Ethambutol	Vancomycin
Nontherapeutic Levels in CSF with or without Inflammation of Meninges	
Aminoglycosides	Cephalosporins (second generation)[c]
Amphotericin B	Doxycycline[d]
β-Lactamase inhibitors[b]	Itraconazole[e]
Cephalosporins (first generation)	

[a]May not achieve therapeutic levels against organisms with higher MIC, as in *Pseudomonas aeruginosa.* Tazobactam does not penetrate the blood–brain barrier.

[b]Includes clavulanic acid, sulbactam, and tazobactam.

[c]Cefuroxime is an exception.

[d]Documented effectiveness for *Borrelia burgdorferi.*

[e]Achieves therapeutic concentrations for *Cryptococcus neoformans* therapy.

TABLE 33-4

Antimicrobial Agents of First Choice and Alternative Choice for Treating Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of

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			Therapy
Gram-Positive Organisms			
S. pneumoniae			10–14 days
Penicillin susceptible MIC ≤0.06 mcg/mL (mg/L)	Penicillin G or ampicillin	Cefotaxime, ceftriaxone, cefepime, or meropenem	
Penicillin resistant MIC >0.06 mcg/mL (mg/L)	Vancomycin[a,b] + cefotaxime or ceftriaxone	Moxifloxacin	
Ceftriaxone resistant MIC >0.5 mcg/mL (mg/L)	Vancomycin[a,b] + cefotaxime or ceftriaxone	Moxifloxacin	
Staphylococcus aureus			14–21 days
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin (A-III) or meropenem	
Methicillin resistant	Vancomycin[a,b]	Trimethoprim-sulfamethoxazole or linezolid	
Group B *Streptococcus*	Penicillin G or ampicillin ± gentamicin[a,b]	Ceftriaxone or cefotaxime	14–21 days
Staphylococcus epidermidis	Vancomycin[a,b]	Linezolid	14–21 days[c]
L. monocytogenes	Penicillin G or ampicillin ± gentamicin[a,b,d]	Trimethoprim-sulfamethoxazole, meropenem	≥21 days
Gram-Negative Organisms			
N. meningitis			7–10 days
Penicillin susceptible	Penicillin G or ampicillin	Cefotaxime or ceftriaxone	
Penicillin resistant	Cefotaxime or ceftriaxone	Meropenem or moxifloxacin	
H. influenzae			7–10 days
β-lactamase negative	Ampicillin	Cefotaxime, ceftriaxone, cefepime, or	

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		moxifloxacin	
β-lactamase positive	Cefotaxime or ceftriaxone	Cefepime or moxifloxacin	
Enterobacterales[e]	Cefotaxime or ceftriaxone	Cefepime, moxifloxacin, meropenem, or aztreonam	21 days
Pseudomonas aeruginosa	Cefepime or ceftazidime ± tobramycin[a,b]	21 days	

[a]Direct CNS administration may be considered if failed conventional treatment.

[b]Monitor serum drug levels.

[c]Based on clinical experience; no clear recommendations.

[d]European guidelines recommend adding gentamicin for the first 7 days of treatment.

[e]Includes *E. coli* and *Klebsiella* spp.

Corticosteroids as an Adjunctive Treatment for Acute Bacterial Meningitis

- In addition to antibiotics, corticosteroids (namely **dexamethasone)** are a commonly used adjunctive therapy in the treatment of acute bacterial meningitis to immunomodulate the inflammatory response.
- Recommendations call for the use of adjunctive dexamethasone in infants and children (6 weeks of age and older) with *H. influenzae* meningitis. The recommended intravenous dose is 0.15 mg/kg every 6 hours for 2–4 days, initiated 10–20 minutes prior to or concomitant with the first dose of antibiotics. In infants and children with pneumococcal meningitis, adjunctive dexamethasone may be considered after weighing the potential benefits and possible risks. If pneumococcal meningitis is suspected or proven, adults should receive dexamethasone 0.15 mg/kg (up to 10 mg) every 6 hours for 2–4 days, with the first dose administered 10–20 minutes prior to first dose of antibiotics.

Neisseria meningitidis (Meningococcus)

- *N. meningitidis* is a leading cause of bacterial meningitis among children and young adults in the United States and around the world. It is spread by direct person-to-person close contact, including respiratory droplets and pharyngeal secretions.
- The presence of petechiae may be the primary clue that the underlying pathogen is *N. meningitidis.* Patients may also have an obvious or subclinical picture of disseminated intravascular coagulation.
- Up to 20% of those with invasive disease may experience sequelae, including extremity loss due to gangrene, deafness, seizures, and other cognitive impairments.
- Third-generation cephalosporins (ie, **cefotaxime** and **ceftriaxone**) are the recommended empiric treatment for meningococcal meningitis. **Penicillin G** or **ampicillin** is recommended for penicillin-susceptible isolates. The recommended duration of therapy is typically 7 days if there is a good clinical response.
- Antimicrobial chemoprophylaxis of close contacts should be started as soon as possible (ideally <24 hours after identification of the index patient). **Ciprofloxacin, ceftriaxone**, and **rifampin** are the most used chemoprophylactic agents.
- For full details on vaccine availability and vaccination recommendations in various age groups and for those with significant risk factors, readers are referred to Chapter 152 of *Pharmacotherapy: A Pathophysiologic Approach*, 12th edition.

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Streptococcus pneumoniae (Pneumococcus or Diplococcus)

- *S. pneumoniae* is a leading cause of community-acquired bacterial meningitis in patients of most age groups.
- Coma, hearing impairment, and seizures are common neurologic complications.
- Penicillin should not be used as empiric therapy if *S. pneumoniae* is suspected. Ceftriaxone and cefotaxime have served as alternatives to penicillin in the treatment of penicillin-nonsusceptible pneumococci. Therapeutic approaches to cephalosporin-resistant pneumococci include the addition of **vancomycin** or, to a lesser extent, rifampin. The combination of vancomycin and ceftriaxone can be used as empirical treatment until antimicrobial susceptibility data are available.
- **Meropenem** is recommended as an alternative to a third-generation cephalosporin in penicillin-nonsusceptible isolates. **Levofloxacin** and **moxifloxacin** represent additional therapeutic options with favorable activity against multidrug-resistant pneumococci and good penetration into the CSF. Intravenous linezolid, daptomycin, and ceftaroline have also emerged as viable therapeutic options for treating multidrug-resistant gram-positive infections.
- Refer to Chapter 49 for information on pneumococcal vaccines.

Haemophilus influenzae Type b (Hib)

- Widespread vaccination of infants and children has effectively decreased the incidence of bacterial meningitis due to Hib in children, resulting in a significant decline in all cases of bacterial meningitis.
- Third-generation cephalosporins (cefotaxime and ceftriaxone) are the drugs of choice for empirical therapy for Hib meningitis as they are active against β-lactamase–producing and non-β-lactamase–producing strains. Cefepime and fluoroquinolones are suitable alternatives regardless of β-lactamase activity.
- Recommended duration of treatment for uncomplicated meningitis is 7 days (adults) or 7–10 days (children).
- Dexamethasone is beneficial for treatment of infants and children with Hib meningitis to diminish the risk of hearing loss, if given before or concurrently with the first dose of antimicrobial agent(s).
- Chemoprophylaxis with rifampin is indicated to reduce the risk of secondary invasive Hib disease in close contacts by eliminating nasopharyngeal and oropharyngeal carriages of *H. influenzae*. Rifampin should be administered orally, once a day for 4 days (20 mg/kg/dose; maximum, 600 mg). For information on who should receive prophylaxis (adults and children), refer to the recommendations of the American Academy of Pediatrics.
- Refer to Chapter 49 for information on *H. influenzae* vaccination.

Listeria monocytogenes

- *L. monocytogenes* causes invasive infections, primarily affecting neonates, the elderly, and individuals with alcohol addiction or immune compromise (including pregnancy), and carries a case-fatality rate of 13%–36% in Western countries.
- Treatment of *L. monocytogenes* meningitis should consist of penicillin G or ampicillin. The addition of aminoglycoside is also recommended in proven infection in both children and adults. Patients should be treated for a minimum of 21 days.
- **Trimethoprim–sulfamethoxazole** and **meropenem** may be effective alternatives because adequate CSF penetration is achieved with these agents.

See Chapter 133, Central Nervous System Infections, authored by Ramy H. Elshaboury, Christina Koutsari, Sarah E. Valiante, and Amir M. Mohareb for a more detailed discussion of this topic.

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